Remarks

With the entry of this amendment, claims 14, 15, 30 and 44-50 are pending and claims 1-13, 16-29, and 31-45 are canceled. Applicants have amended claims 46 and 48.

Rejections under 35 USC § 112

Applicants traverse the rejections under Section 112 for the following reasons.

The Federal Circuit has held that "a considerable amount of experimentation is permissible, if it is merely routine, **or** if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ.2d 1400, 1404 (1988). (Emphasis added.) Applicants have argued that in light of the specification and state of the art, using the present compounds for the present claims would be a matter of routine experimentation, achievable by one of ordinary skill in the art without undue experimentation. To further strengthen the record that the specification is enabled for the claimed methods, applicants provide these additional references for the Examiner's consideration.

The reference Peptides 20 (1999), pp.1247 – 1262 (Appendix 1) discloses that a LHRH antagonist such as Certrorelix is effective for treating gynecological diseases such as multiocular ovary syndrome and hysteromyoma (section 1.7., pp. 1251- 1252); non-oncological diseases such as precocious puberty (section 1.8., p. 1252); oncological diseases such as uterine cancer, breast cancer, and prostatic cancer (section 2, pp. 1252 - 1256).

The reference Human Reproduction Update. 2000, Vol. 6, No. 4, pp.322 - 331 (Appendix 2) discloses that a LHRH antagonist (Certrorelix) is effective for treating hysteromyoma, endometriosis and prostatic cancer (abstract and p. 328).

The website of TAP (http://www.tap.com/prd_ldep.asp) (Appendix 3) discloses that Lupron Depo (Leuplin) is effective for treating prostatic cancer, endometriosis, precocious puberty and the like. The sales of Lupron Depot in the US started in 1989 (see the attached printout of the website of Takeda Pharmaceutical Company Limited).

The GnRH (LHRH) agonist acts on the receptor on the cell membrane of gonadotrophin (Gn) producing cell in anterior pituitary gland to cause release of Gn (LH and the like) into the blood. However, when GnRH is present in excess, or when an agonist (superagonist) having an activity far stronger (not less than 10-fold) than GnRH in the body, like Leuplin, acts, the receptor on the cell membrane of Gn producing cell disappears from the surface of cell membrane (taken into cytoplasm: internalization), thus stopping the release of Gn into the blood. This state affords the same efficacy as suppression of GnRH activity by GnRII antagonist. In other words, GnRH superagonists such as Leuplin and GnRH (LHRH) antagonists afford the same efficacy.

WO 96/24597 (Appendix 4) discloses that Leuplin (Leuprorelin acetate) has been used as a therapeutic agent for sex hormone dependent cancers, various gynecological diseases and the like by suppressing the secretion of sex hormones (p.2, lines 6 - 28), and the LHRH antagonist compound (1) can be used for suppressing the secretion of sex hormone and is effective as a therapeutic agent for sex hormone dependent cancers, various gynecological diseases and the like (p.33, line 22 - p.34, line 7).

Applicants also repeat below the arguments of record that were presented in the Response filed January 30, 2004.

The level of one of ordinary skill in the art is high. For example, the artisan of ordinary skill who would generally practice the invention would likely be a Ph.D. and/or M.D. specializing in pharmacology. An artisan of such a high skill level would easily be capable of testing the compounds against any of the claimed disorders or biological functions and optimizing the appropriate dosage level. The skilled artisan, in light of the specification, would have sufficient knowledge to practice the invention at the time of filing.

The specification provides guidance on how to use the invention. Pages 120-126 provide guidance on the therapeutic use of the invention. Based on the guidance provided in the specification, one of skill in the art could have assayed the compounds of the present invention in known *in vivo* or *in vitro* models for the disorders of the present claims. The relative routine nature of such testing is supported by the previously attached article, by Zhu *et al.*, Bioorganic & Medicinal Chemistry Letters 12 (2002) 403-406.

The Examiner has misconstrued the level of unpredictability in the art, which does not rise to the level of requiring undue experimentation. The Huirne and Lambalk Lancet reference cited by the Examiner actually supports that one of skill in the art could have practiced the claimed methods. As noted in this reference "GnRH-receptor antagonists, that immediately block GnRH's effects, [have recently] been developed for clinical use with acceptable pharmacokinetic, safety and commercial profiles." The authors continue that "[a]ll current indications for Gn-RH-agonists desensitizations may prove to be indications a GnRH-receptor antagonist, including endometriosis, leiomyoma, and breast cancer in women, benign prostatic hypertrophy and prostatic carcinoma in men, and central precocious puberty in children."

The fact that the "best *clinical evidence* so far has been in assisted reproduction and prostate cancer" does not mean the present invention is not enabled. (Emphasis added.) As noted in the below summary from MPEP § 2107.02 IV, the need for clinical trials and data is regulatory and separate from the 35 USC § 112 statutory requirement of the USPTO.

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims. *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991) (human clinical data is not required to demonstrate the utility of the claimed invention, even though those skilled in the art might not accept other evidence to establish the efficacy of the claimed therapeutic compositions and the operativeness of the claimed methods of treating humans).

Conclusion

Applicants submit that the present application is now in condition for allowance, and favorable reconsideration thereof is respectfully requested. If the Examiner believes that an interview would advance prosecution of the application, he is invited to contact the

undersigned by telephone. If there are any unaccounted fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741.

Respectfully submitted,

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